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(56) and (58) continued overleaf

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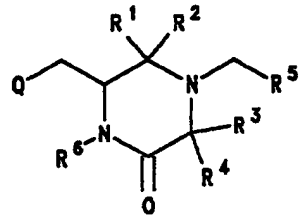
(54) Piperazine derivatives

(57) Compounds of formula (I), and salts and prodrugs thereof



(I)

wherein

Q represents a phenyl group substituted by one or more halo, optionally substituted naphthyl, indolyl, benzthiophenyl, benzofuranyl, benzyl or fluorenyl;

R^1 and R^2 each represent H, or R^1 and R^2 together form a group =O;

one of R^3 and R^4 represents H and the other is selected from H, optionally substituted phenyl and optionally substituted benzyl, or R^3 and R^4 together form a group =O;

R^5 optionally substituted phenyl; and

R^6 is H or optionally substituted benzyl;

with the proviso that when R^3 and R^4 together form =O, and only when R^3 and R^4 together form =O, R^1 and R^2 each represent H; are tachykinin receptor antagonists useful in therapy.

GB 2 271 774 A

(56) Documents Cited
Chemical Abstracts 53:11397b Chemical Abstracts 52: 2748f Bull Chem.Soc. Japan, 58(5) 1413-20,(1985) and Chemical Abstracts 104:109574g Indian J. Chem., Sect. B 29B(2) 197-9 (1990) and Chemical Abstracts 113: 78332f Tetrahedron 47(30), 5643-66, (1991) and Chemical Abstracts 115:232581m

(58) Field of Search
UK CL (Edition L) **C2C CTR CTW**
INT CL^{5} **C07D**
ONLINE DATABASES: CAS ONLINE

1,4-PIPERAZINE DERIVATIVES

This invention relates to a class of 1,4-piperazine derivatives, which are useful as tachykinin receptor antagonists.

The tachykinins are a group of naturally-occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in the peripheral nervous and circulatory systems. The three known mammalian tachykinins are: substance P, neurokinin A and neurokinin B:

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardivascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitus, inflammatory diseases of the gut including ulcerative colitis and Crohn disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists", C.A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, J. Auton. Pharmacol. (1993) 13, 23-93. Tachykinin antagonists are also believed to be useful in allergic conditions [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9], and as anticonvulsants [Garant et al., Brain

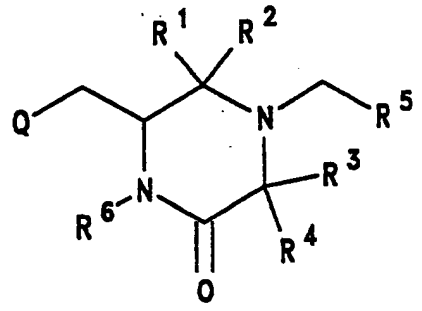
Research (1986) 382 372-8]. Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon et al., Cancer Research (1992) 52, 4554-7].

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosis (European patent application no. 0 436 334), conjuctivitis, vernal conjunctivitis, contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989) and emesis (European patent application no. 0 533 280).

We have now found a class of non-peptides which are potent antagonists of tachykinins.

European patent application no. 0428434 discloses tachykinin receptor antagonists comprising, inter alia, a 1,4-piperazine moiety and two aryl moieties. The compounds are structurally remote from those of the present invention.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

Q represents a phenyl group substituted by one or more halo, optionally substituted naphthyl, optionally substituted indolyl, optionally substituted benzthiophenyl, optionally substituted benzofuranyl, optionally substituted benzyl or optionally substituted fluorenyl;

R^1 and R^2 each represent H, or R^1 and R^2 together form a group =O;

one of R^3 and R^4 represents H and the other is selected from H, optionally substituted phenyl and optionally substituted benzyl, or R^3 and R^4 together form a group =O;

R^5 represents phenyl optionally substituted by 1, 2, or 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a, SOR^a, NR^aR^b, NR^aCOR^b, $NR^aCO_2R^b$, CO_2R^a or $CONR^aR^b$, where R^a and R^b independently represent H, C_{1-6}alkyl, phenyl or trifluoromethyl; and

R^6 represents H or optionally substituted benzyl;

with the proviso that when R^3 and R^4 together form =O, and only when R^3 and R^4 together form =O, R^1 and R^2 each represent H.

As used herein, the definition of each expression, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The alkyl, alkenyl and alkynyl groups referred to with respect to any of the above formulae may represent straight, branched or cyclic groups or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo, especially chloro and fluoro.

Where Q represents optionally substituted fluorenyl, the group is linked through the bridgehead carbon atom, that is to say, C-9.

Where Q represents optionally substituted naphthyl, indolyl, benzothiophenyl, benzofuranyl, benzyl or fluorenyl, suitable substituents include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a, SOR^a, SO_2R^a, OR^a, NR^aR^b, NR^aCOR^b, NR^aCOOR^b, $COOR^a$ or $CONR^aR^b$, where R^a and R^b are as above defined. One or more substituents may be present and each may be located at any available ring position, except, where Q is optionally substituted indolyl, the nitrogen atom. Where Q is optionally substituted indolyl, suitable nitrogen substituents include C_{1-6}alkyl, optinally substituted phenyl(C_{1-4}alkyl), $COOR^a$ or $CONR^aR^b$, wherein R^a and R^b are as above defined.

Suitable values of the group Q include 3,4-dichlorophenyl, 3-indolyl, 2-naphthyl, 3-naphthyl, 9-fluorenyl, benzyl, 3-benzothiophenyl and 3-benzofuranyl.

Preferably Q is 3-indolyl, 3-benzothiophenyl or 3,4-dichlorophenyl, more preferably 3-indolyl.

When one of R^3 and R^4 represents substituted phenyl or substituted benzyl, suitable substituents include C_{1-6}alkyl, C_{1-6}alkoxy, halo, cyano, nitro, trifluoromethyl and trimethylsilyl.

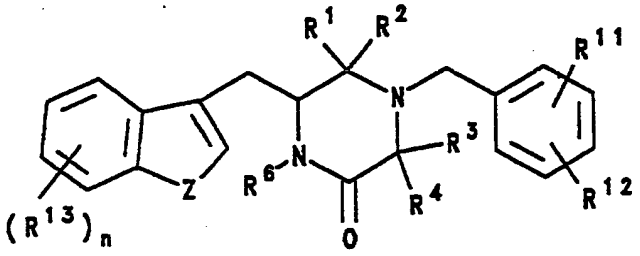
Preferred are compounds according to the invention wherein R^3 and R^4 together form a group =O (and R^1 and R^2 each represents H).

When R^5 represents substituted phenyl, suitable phenyl substituents include nitro, trifluoromethyl, trimethylsilyl, bromo, chloro, fluoro, iodo, cyano, methyl, ethyl, cyclopropyl, vinyl, methoxy, phenoxy and amino.

Preferably R^5 represents phenyl substituted by one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo and trifluoromethyl. More preferably R^5 represents 3,5-dimethylphenyl or 3,5-bistriflouoromethyl phenyl.

When R^6 represents substituted benzyl, suitable substituents include C_{1-6}alkoxy, halo, nitro, trifluoromethyl and trimethylsilyl. Preferably R^6 represents H or unsubstituted benzyl, more preferably H.

A particular subgroup of compounds according to the invention is represented by compounds of formula (Ia), and salts and prodrugs thereof:



(Ia)

wherein R^1, R^2, R^3, R^4 and R^6 are as defined for formula (I);

Z represents O, S or NR^{14} (where R^{14} is H, C_{1-6}alkyl, optionally substituted phenyl(C_{1-4}alkyl), CO_2R^a or $CONR^aR^b$, where R^a and R^b are as previously defined), preferably S, NH or NCH_2Ph, more preferably NH;

R^{11} and R^{12} each independently represent H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl or OR^a where R^a and R^b are as previously defined;

each R^{13} may occupy any available carbon atom of the bicyclic ring system and independently represents C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl or OR^a where R^a and R^b are as previously defined; and

n is 0, 1, 2 or 3, preferably 0.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by

mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible <u>in vivo</u> into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention may exist both as enantiomers and as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The substance P antagonising activity of the compounds described herein was evaluated using the human NK1R assay described in published European patent application no. 0 528 495. Substance P receptor antagonism was demonstrated for the compounds of the Examples.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or topical administration including administration by inhalation or insufflation.

The invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), or a salt or prodrug thereof, and a pharmaceutically acceptable carrier, which process comprises bringing a compound of formula (I), or a salt or prodrug thereof into association with a pharmaceutically acceptable carrier.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active

ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are adminsitered by the oral or nasal respiratory route

for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For topical administration, for example as a cream, ointment or lotion, pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotropic lateral sclerosis (ALS; Lou Gehrig's disease) and other neuropathological disorders such as peripheral neuropathy, for example, diabetic or chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinoma such as small cell lung cancer; respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, irritable bowel syndrome, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like, and proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis; oedema, such as oedema caused by thermal injury; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders

associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, surgery, migraine and variations in intercranial pressure; disorders of bladder function such as cystitis and bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and especially migraine.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a

tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

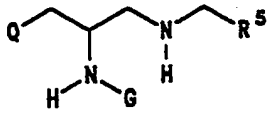
For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2-adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

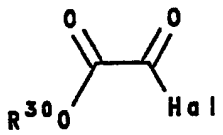
The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day. For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

Compounds of formula (I) wherein R^1 and R^2 represent H may be prepared by reaction of a compound of formula (II) with a compound of formula (III):



(II)



(III)

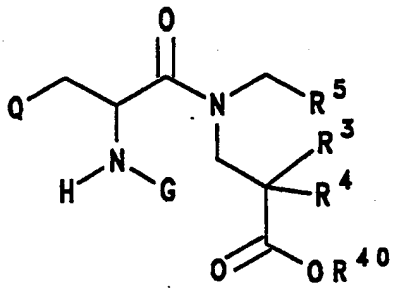
wherein Q and R^5 are as defined for formula (I), G is a protecting group, R^{30} is alkyl and Hal is halo, such as chloro, bromo or iodo, in the presence of a base.

Suitable bases of use in the reaction include tertiary amines such as, for example, triethylamine.

Suitable protecting groups include t-butoxycarbonyl (Boc).

Suitably R^{30} represents methyl and Hal represents chloro.

Compounds of formula (I) wherein R^1 and R^2 together form =O may be prepared by cyclisation of an intermediate of formula (IV):



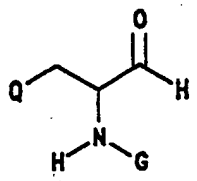
(IV)

wherein Q and R^5 are as defined for formula (I), R^3 and R^4 are as defined for formula (I) other than =O, G is as defined for formula (II), and R^{40} represents alkyl, followed by deprotection.

The cyclisation is conveniently effected by acid catalysis, for example, using a mineral acid, such as hydrochloric acid, in a suitable solvent, such as an alcohol, for example, methanol.

Compounds of formula (I) may also be prepared from other compounds of formula (I). For example, compounds of formula (I) wherein R^6 is optionally substituted benzyl may be prepared from compounds of formula (I) wherein R^6 is H by reaction with an optionally substituted benzylating reagent, such as, for example, a benzyl halide.

Compounds of formula (II) may be prepared by reductive amination of an aldehyde of formula (V)

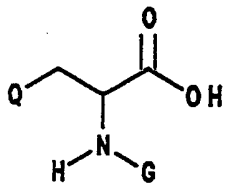


(V)

wherein Q and G are as previously described with an amine of formula $H_2NCH_2R^5$, wherein R^5 is as previously defined.

Suitable rection conditions will be readily apparent to those skilled in the art.

Aldehydes of formula (V) may be prepared from the corresponding amino acid of formula (VI).



(VI)

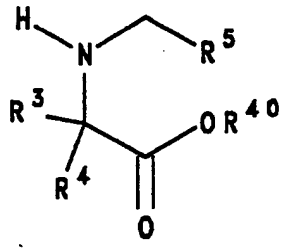
wherein Q and G are as previously defined, or an ester or amide thereof, by reduction.

Suitable reducing agents will be readily identified by those skilled in the art.

Compounds of formula (VI) may be prepared from the corresponding unprotected compounds (wherein G is replaced by H) by conventional methods, for example, reaction with Boc - chloride or Boc - anhydride. The unprotected compounds are commercially available, or may be prepared from commercially available starting materials by conventional methods. Conventional procedures for the preparation of amino acids are well documented and are described, for example, in Chemistry and Biochemistry of the Amino Acids, ed. G. C. Barrett, Chapman and Hall, 1985.

Compounds of formula (III) are commercially available.

Intermediates of formula (IV) may be prepared by reaction of a compound of formula (VI) with a compound of formula (VII):

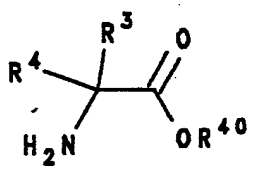


(VII)

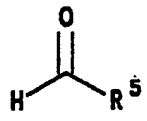
wherein Q, R^3, R^4, R^5, R^{40} and G are as defined for formula (IV) above.

The reaction is effected under conventional peptide coupling conditions. Suitable conditions are described in the accompanying examples. Other suitable conditions will be readily apparent to those skilled in the art.

Compounds of formula (VII) may be prepared by reaction of a compound of formula (IX) with a compound of formula (X):



(IX)



(X)

wherein R^3, R^4, R^5 and R^{40} are as defined for formula (IV), followed by reduction.

Suitable reducing agents of use in the reduction include hydride reducing agents, such as alkali metal borohydrides, for example sodium cyanoborohydride.

Compounds of formulae (IX) and (X) are commercially available, or may be prepared from

commercially available starting materials by known methods.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wutts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following non-limiting Examples illustrate the preparation of compounds according to the invention.

EXAMPLE 1

1-(3,5-Bis(trifluoromethyl)benzyl)-2,5-dioxo-3-((3-indolyl) methyl)-1,4-piperazine

To L-tryptophan methyl ester hydrochloride (3.58g, 14mmol) and dichloromethane (35ml) at 0°C was added aqueous sodium hydroxide (1.4g dissolved in 35ml water). To the vigorously stirred mixture at 0°C was added chloroacetylchloride (2.4g). The mixture was allowed to warm to room temperature and stirred for a further 18 hours. After dilution with dichloromethane (30ml), the aqueous layer was removed, and the organic layer washed with 1M aqueous hydrochloric acid, water, and then dried ($MgSO_4$). The solvents were evaporated and the residual oil treated with ethoxyethanol (35ml) and 3,5-bis(trifluoromethyl)benzylamine (3.37g). The resulting solution was heated at reflux for 24 hours. On cooling, the solvent was evaporated at reduced pressure, and the residue chromatographed on silica (eluent neat ethyl acetate), to give 1-(3,5-bis(trifluoromethyl)benzyl-2,5- dioxo-3-((3-indolyl)methyl)-1,4-piperazine. ^1H NMR (360MHz; $CDCl_3$) δ 2.93 (1H, d, J = 16.9Hz), 3.37 (2H, m), 3.47 (1H, d, J = 17Hz), 3.88 (1H, d, J = 15.1Hz), 4.41 (1H, m), 4.84 (1H, d, J = 15.1Hz), 6.16 (1H, s), 7.04 (1H, d, J = 2.1Hz), 7.14 (1H, t, J = 7.5Hz), 7.22 (1H, t, J = 7.2Hz), 7.38 (1H, d, J = 7.2Hz), 7.60 (3H, m), 7.81 (1H, s), 8.18 (1H, s). m/e (CI^+) 470 (M^+H). Found: C, 56.15; H, 3.83; N, 8.86. $C_{22}H_{17}N_3F_6O_2$ requires C, 56.30; H, 3.65; N, 8.95%.

EXAMPLE 2

1-(3,5-Bis(trifluoromethyl)benzyl)-2,5-dioxo-3-((3-indolyl) methyl)-6- phenyl-1,4-piperazine

a. d,l α-Phenylglycine (20g) was added to a saturated solution of hydrogen chloride in dry methanol (250ml). The mixture was stirred at room temperature for 72 hours. Evaporation of the solvent afforded methyl α-aminophenylacetate hydrochloride.

b. To the product of Example 2(a) (4.16g) in CH_2Cl_2 (50ml) was added with stirring, 3,5-bis(trifluoromethyl) benzaldehyde (5g), and anhydrous $MgSO_4$ (25g). To the stirred mixture was added triethylamine (2.9ml), and stirring continued for a further 36 hours. The solids were then removed by filtration, and the filtrate concentrated at reduced pressure. The residue was dissolved in dry methanol (15ml), and sodium borohydride (1.42g) was added portionwise with stirring. After stirring an additional 2 hours at room temperature, the solvents were evaporated and the residue partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue was dissolved in dry diethyl ether, and a solution of oxalic acid (1.85g) in dry diethyl ether (30ml) was added. The precipitate was collected by filtration to afford methyl α-(3,5-bis(trifluoromethyl) benzylamino)-phenylacetate oxalate. ^1H NMR (250MHz; DMSO) δ 3.61 (3H, s), 3.91 (2H, ABQ), 4.53 (1H, s), 7.42 (5H, m), 7.96 (1H, s), 8.02 (2H, s).

c. To N-^{t}Butoxycarbonyl-L-tryptophan (2.56g) in dry CH_2Cl_2 (17ml) under an argon atmosphere, was added with stirring, dry

triethylamine (1.18ml). The resulting solution was cooled to 0°C and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (2.14g) added. After stirring the resulting mixture for 30 minutes at 0°C, the product of Example 2(b) (3.4g) and triethylamine (2.4ml) were added. After stirring at room temperature for 72 hours, the mixture was poured into saturated aqueous $NaHCO_3$, extracted with dichloromethane, the extracts dried ($MgSO_4$) and evaporated. The residue was dissolved in saturated methanolic hydrogen chloride (20ml), and allowed to stand at room temperature for 24 hours. The solvent was evaporated and the residue treated with excess saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), evaporated, and the residue chromatographed on silica gel (eluent gradient 50% diethyl ether:ethyl acetate to neat ethyl acetate) to afford two diastereoisomeric diketo piperazines: 1-(3,5-Bis(trifluoromethyl)benzyl)-2,5-dioxo-3-((3-indolyl)methyl)-6-phenyl-1,4-piperazine.

Diastereoisomer A (L733,059). ^1H NMR (360MHz; $CDCl_3$) δ 3.17 (1H, dd, J = 14.7, 9.4Hz), 3.82 (1H, dd, J = 14.7, 3.2Hz), 4.05 (1H, d, J = 14.7Hz), 4.53 (1H, dd, J = 9.7, 3.5Hz), 4.71 (1H, s), 5.18 (1H, d, J = 14.7Hz), 5.87 (1H, s), 7.12-7.40 (11H, m), 7.56 (2H, s), 7.63 (1H, d, J = 7.8Hz), 7.78 (1H, s), 8.14 (1H, s). m/e (Cl^-) 544 (M-H).

Diastereoisomer B (L733,141). ^1H NMR (360MHz; $CDCl_3$) δ 3.16 (1H, dd, J = 14.4, 9.7Hz), 3.80 (1H, dd, J = 14.6, 3.2Hz), 4.04 (1H, d, J = 15.0Hz), 4.52 (1H, dd, J = 9.7, 3.5Hz), 4.70 (1H, s), 5.17 (1H, d, J = 15.0Hz), 5.86 (1H, s), 7.10-7.40 (11H, m), 7.55 (2H, s), 7.62 (1H, d, J = 8Hz), 7.77 (1H, s), 8.14 (1H, s). m/e (Cl^-) 545 (M^+).

EXAMPLE 3

4-Benzyl-1-(3,5-bis(trifluoromethyl)benzyl)-2,5-dioxo-3-((3-indolyl) methyl)-1,4-piperazine

and 1-(3,5-bis(trifluoromethyl)benzyl)-3-((N-benzyl-3-indolyl)methyl)-2,5- dioxo-1,4-piperazine

To the product of Example 1 (858mg) in dry tetrahydrofuran (5ml) under an argon atmosphere, was added sodium hydride (120mg of a 60% dispersion in oil), followed by benzyl bromide (240µL). The resulting mixture was stirred at room temperature for 36 hours, then partitioned between aqueous NH_4Cl and ethyl acetate. The organic layer was separated, dried ($MgSO_4$), evaporated, and the residue chromatographed on silica gel (eluent diethyl ether) to afford two regioisomeric benzylated derivatives.

4-benzyl-1-(3,5-bis(trifluoromethyl)benzyl)-2,5-dioxo-3-((3-indolyl) methyl)-1,4-piperazine. ^1H NMR (360MHz; $CDCl_3$) δ 2.20 (1H, d, J = 16.9Hz), 3.18 (1H, d, J = 16.9Hz), 3.20 (1H, d, J = 15.2Hz), 3.28 (1H, dd, J = 14.8, 4.5Hz), 3.54 (1H, dd, J = 14.8, 3.0Hz), 4.05 (1H,d, J = 14.7Hz), 4.29 (1H, t, J = 3.6Hz), 4.96 (1H, d, J = 15.2Hz), 5.44 (1H, d, J = 14.8Hz), 6.87 (1H, d, J = 2.4Hz), 7.12 (1H, t, J = 7.1Hz), 7.21 (1H, t, J = 7.5Hz), 7.28 (2H, m), 7.31-7.4 (3H, m), 7.47 (2H, s), 7.52 (1H, d, J = 7.9Hz), 7.77 (1H, s), 8.12 (1H, s). m/e (Cl^-) 559 (M^+). Found: C, 62.38; H, 4.29; N, 7.37. $C_{29}H_{23}N_3F_6O_2$ requires C, 62.25; H, 4.14; N, 7.51%

1-(3,5-Bis(trifluoromethyl)benzyl)-3-((N-benzyl-3-indolyl) methyl-2,5- dioxo-1,4-piperazine. ^1H NMR (360MHz; $CDCl_3$) δ 2.40 (1H, dd, J = 11.2, 12.7Hz), 2.76 (1H, dd, J = 12.7, 5.9Hz), 3.01 (2H, ABQ), 3.70 (1H, d, J = 16.7Hz), 3.96 (1H, dd, J = 16.7,

1.8Hz), 4.04 (1H, dd, J = 11.2, 5.8Hz), 4.37 (1H, d, J = 14.9Hz), 4.90 (1H, d, J = 14.8Hz), 5.42 (1H, s), 6.58 (1H, d, J = 7.7Hz), 6.75 (1H, t, J = 7.4Hz), 6.84 (1H, d, J = 7.2Hz), 7.03-7.12 (3H, m), 7.24-7.27 (4H, m), 7.66 (2H, s), 7.82 (1H, s). m/e (Cl^-) 559 (M^+).

EXAMPLE 4

1-(3,5-Bistrifluoromethylbenzyl)-2,3-dioxo-5-(3-indolyl)-1,4-piperazine

a. N-α-BOC-L-Tryptophan (15.2g, 100mmol) in dichloromethane (400ml) with triethylamine (20ml) was cooled to -30°C and treated with isobutyl chloroformate (6.9, 50mmol). The mixture was stirred at -30°C for 15 minutes, allowed to warm to 0°C and then N,O-dimethylhydroxylamine hydrochloride (5.37g, 100mmol) was added in one portion. The reaction was stirred for one hour and then washed with water (50ml), 10% citric acid solution (50ml), water (50ml), saturated sodium bicarbonate solution (50ml) and water (50ml). The organic solution was dried ($MgSO_4$), filtered through a small pad of silica and evaporated to yield a white solid (9.5g).

b. N-(3,5-Bistrifluoromethylbenzyl)-2-(t-butyloxy carbonylamino) propylamine

The product of Example 4(a) in tetrahydrofuran (200ml) was cooled to -10°C and treated dropwise with lithium aluminium hydride (1M in ether, 15ml). The reaction was stirred for two hours at -50°C and then cautiously quenched with 20% citric acid solution. The reaction mixture was poured into ethyl acetate and washed with water, saturated sodium bicarbonate and then water. The organic layer was separated,

dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in dichloromethane, and magnesium sulphate (10g) and 3,5-bistrifluoromethyl benzylamine (6.3g, 26mmol) were added. The reaction was stirred for 16 hours before filtering and evaporating. The residue was dissolved in methanol and treated with excess sodium borohydride at 5°C. The reaction was stirred for one hour, before evaporating the solvent and partitioning the residue between ethyl acetate and water. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography on silica using ethyl acetate to yield the product (5.2g). NMR (360MHz, $CDCl_3$) δ 8.04 (1H, s), 7.75 (3H, s), 7.62 (1H, d, J = 7Hz), 7.35 (1H, d, J = 7Hz), 7.18 (1H, t, J = 7Hz), 7.10 (1H, t, J = 7Hz), 7.01 (1H, s), 4.68 (1H, bs), 4.11 (1H, bs), 3.83 (2H, ABQ), 3.00-2.92 (2H, m), 2.73 (1H, dd, J = 5 and 12Hz), 2.65 (1H, dd, J = 6 and 13), 1.42 (9H, s).

c. 1-(3,5-Bistrifluoromethylbenzyl)-2,3-dioxo-5-(3-indolyl)-1,4-piperazine

The product of Example 4(b) (2.0g) was dissolved in dichloromethane (200ml) with triethylamine (1.0g) and treated with methyl oxalyl chloride (400mg). The reaction was stirred for one hour before evaporating the solvent and dissolving the residue in methanolic hydrogen chloride solution. The reaction was stirred for 16 hours and the solvent was removed and the residue was partitioned between ethyl acetate and potassium carbonate. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on silica to yield 0.65g. NMR (360MHz, D_6 DMSO) δ 10.89 (1H, s), 8.77 (1H, d, J = 2Hz), 8.01 (1H, s), 7.98 (2H, s), 7.44 (1H, d, J = 7Hz), 7.33 (1H, d, J = $7H_2$), 7.08 (1H, t, J = 7Hz), 6.97 (1H, t, J = 7Hz), 7.70 (2H, ABQ), 3.91 (1H, bs), 3.56 (1H, dd, J = 4 and 13Hz), 3.54-3.31 (1H, m), 2.95 (1H, dd, J = 5Hz and 14Hz), 2.78

(1H, dd, J = 8 and 15Hz). Found: C, 56.46; H, 3.64; N, 8.86; $C_{22}H_{17}F_6N_3O_2$ requires C, 56.30; H, 3.65; N, 8.95%.

EXAMPLE 5

6-Benzyl-1-(3,5-dimethylbenzyl)-2,5-dioxo-3-((3-indolyl)methyl)-1,4- piperazine

a. Methyl 2-((3,5-dimethylbenzyl)amino)-3-phenyl-propionate

Triethylamine (1.39ml) was added to a suspension of L-phenylalanine methyl ester hydrochloride (2.15g) in dichloromethane (35ml). After stirring for 10 minutes at room temperature, 3,5-dimethylbenzaldehyde (1.35g) was added, followed by anhydrous magnesium sulphate (1g). The solution was stirred for 16 hours, filtered and the solvents were removed *in vacuo* to yield the title compound as an oil.

b. Methyl 2-((3,5-dimethylbenzyl)amino-3-phenyl-propionate

The product of Example 5(a) was dissolved in methanol (35ml). To this solution, at 0°C, was added sodium cyanoborohydride (0.95g) in small portions over 10 minutes. The resulting solution was stirred for 16 hours at room temperature. The solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous sodium sulphate, and the solvents were removed *in vacuo* to yield the title compound as a colourless oil (2.28g).

c. N-(3,5-Dimethylbenzyl)-N-((2-(methoxycarbonyl)-3-phenyl)ethyl)- 3-(3-indolyl)-2-((tert-butoxycarbonyl)amino)-propionamide

Isobutylchloroformate (0.65ml) was added to a solution of N-BOC-L-tryptophan (1.53g) in dichloromethane (15ml) containing N-methyl piperidine (0.61ml) at -20°C under a nitrogen atmosphere. After 30 minutes stirring at -20°C methyl 2-((3,5-dimethylbenzyl)amino)-3-phenyl-propionate (1.5g) was added. The solution was stirred for 16 hours at room temperature, washed with (a) water, (b) 10% citric acid solution, (c) brine, (d) sodium bicarbonate solution and (e) brine. The solution was dried over anhydrous sodium sulphate. Removal of the solvent in vacuo gave the title compound as a yellow oil.

d. N-(3,5-Dimethylbenzyl)-N-((2-(methoxycarbonyl)-3-phenyl)ethyl)-3-(3-indolyl)-2-amino-propionamide

The product of Example 5(c) was dissolved in methanolic hydrogen chloride solution (130mls) and the resulting solution was stirred for 16 hours. The solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was dried over anhydrous potassium carbonate and removal of the solvent *in vacuo* gave the title compound as an off-white solid.

e. 6-Benzyl-1-(3,5-dimethyl benzyl)-2,5-dioxo-3-((3-indolyl)methyl)-1,4-piperazine

The product of Example 5(d) (2.5g) was dissolved in toluene (25mls) and stirred at room temperature for 16 hours under an inert atmosphere. Removal of the solvent *in vacuo* and chromatography of the residue on silica gel (eluent 50% ethyl

acetate/petrol) gave the title compound as a white solid after recrystallisation from benzene/petrol. Mp = 107-109.5°C, EI^+ mass m/e: 451.2275 (M^+). $C_{29}H_{29}N_3O_2$ requires m/z 451.2260. ^1H NMR (360MHz, $CDCl_3$) δ 8.04 (1H, s), 7.52 (1H, d, J = 7.9Hz), 7.43 (2H, d, J = 7.11Hz), 7.33 (1H, d), 7.32 (1H, dd), 7.19 (1H, dd), 7.18 (2H, d), 7.10 (1H, dd), 6.94 (1H, s), 6.87 (2H, s), 6.76 (1H, d, J = 2.2Hz), 5.68 (1H, d, J = 14.6Hz), 5.65 (1H, s), 4.18 (1H, dd, J = 4.05Hz and 4.05Hz), 4.10 (1H, dd, J = 11.20 and 2.6Hz), 3.86 (1H, d, J = 14.6Hz), 3.24 (1H, dd, J = 14.1 and 4.5Hz), 3.15 (1H, m), 3.14 (1H, m), 2.29 (6H, s), 1.12 (1H, dd, J = 14.2 and 11.2Hz).

The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 6A Tablets containing 1-25mg of compound

	Amount mg		
Compound of formula (I)	1.0	2.0	25.0
Microcrystalline cellulose	20.0	20.0	20.0
Modified food corn starch	20.0	20.0	20.0
Lactose	58.5	57.5	34.5
Magnesium Stearate	0.5	0.5	0.5

EXAMPLE 6B Tablets containing 26-100mg of compound

	Amount mg		
Compound of formula (I)	26.0	50.0	100.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	213.5	189.5	139.5
Magnesium Stearate	0.5	0.5	0.5

The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

EXAMPLE 7 Parenteral injection

	Amount mg
Compound of formula (I)	1 to 100mg
Citric Acid Monohydrate	0.75mg
Sodium Phosphate	4.5mg
Sodium Chloride	9mg
Water for Injections	to 1ml

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

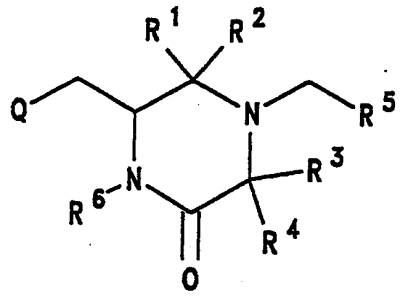
EXAMPLE 8 Topical formulation

	Amount mg
Compound of formula (I)	1-10g
Emulsifying Wax	30g
Liquid paraffin	20g
White Soft Paraffin	to 100g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

CLAIMS:

1. A compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

Q represents a phenyl group substituted by one or more halo, optionally substituted naphthyl, optionally substituted indolyl, optionally substituted benzthiophenyl, optionally substituted benzofuranyl, optionally substituted benzyl or optionally substituted fluorenyl;

R^1 and R^2 each represent H, or R^1 and R^2 together form a group =O;

one of R^3 and R^4 represents H and the other is selected from H, optionally substituted phenyl and optionally substituted benzyl, or R^3 and R^4 together form a group =O;

R^5 represents phenyl optionally substituted by 1, 2, or 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a, SOR^a, NR^aR^b, NR^aCOR^b, $NR^aCO_2R^b$, CO_2R^a or $CONR^aR^b$, where R^a and R^b independently represent H, C_{1-6}alkyl, phenyl or trifluoromethyl; and

R^6 represents H or optionally substituted benzyl;

with the proviso that when R^3 and R^4 together form =O, and only when R^3 and R^4 together form =O, R^1 and R^2 each represent H.

2. A compound as claimed in claim 1 wherein Q is 3-indolyl, 3-benzothiophenyl or 3,4-dichlophenyl.

3. A compound as claimed in claim 2 wherein Q is 3-indolyl.

4. A compound as claimed in any preceding claim wherein R^1 and R^2 both represent H, and R^3 and R^4 together represent =O.

5. A compound as claimed in any preceding claim wherein R^5 represents phenyl substituted by one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo and trifluoromethyl.

6. A compound as claimed in any preceding claim wherein R^6 is H or unsubstituted benzyl.

7. A compound as claimed in claim 1 selected from:
1-(3,5-bis(trifluoromethyl)benzyl)-2,5-dioxo-3-((3-indolyl)methyl)-1,4-piperazine;
1-(3,5-bis(trifluoromethyl)benzyl)-2,5-dioxo-3-((3-indolyl)methyl)-6-phenyl-1,4-piperazine;
4-benzyl-1-(3,5-bis(trifluoromethyl)benzyl)-2,5-dioxo-3-((3-indolyl)methyl)-1,4-piperazine;
1-(3,5-bis(trifluoromethyl)benzyl)-3-((N-benzyl-3-indolyl)methyl)-2,5-dioxo-1,4-piperazine;

1-(3,5-bis(trifluoromethyl)benzyl)-2,3-dioxo-5-((3-indolyl)methyl)-1,4-piperazine;
6-benzyl-1-(3,5-dimethylbenzyl)-2,5-dioxo-3-((3-indolyl)methyl)-1,4-piperazine;
and salts and prodrugs thereof.

8. A compound as claimed in any preceding claim for use in therapy.

9. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 7 and a pharmaceutically acceptable carrier therefor.

10. The use of a compound as claimed in any of claims 1 to 7 for the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins.

11. The use of a compound as claimed in any of claims 1 to 7 for the manufacture of a medicament for the treatment of pain or inflammation.

12. The use of a compound as claimed in any of claims 1 to 7 for the manufacture of a medicament for the treatment of migraine.

Patents Act 1977 Examiner's report to the Comptroller under Section 17 (The Search report)	33	Application number GB 9321855.0
Relevant Technical Fields (i) UK Cl (Ed.M) C2C CTR CTW (ii) Int Cl (Ed.5) C07D Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE DATABASE: CAS ONLINE		Search Examiner D S LUCAS Date of completion of Search 16 December 1993 Documents considered relevant following a search in respect of Claims :- 1-12

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
X	Tetrahedron 47 (30). 5643-66 (1991) and Chemical Abstracts 115: 232581m (EMORY UNIV) see particularly compounds with reg numbers 137023-19-9 and 137023-07-5	1,6, 8 and 9
X	Indian J Chem. Section B 29B(2) 197-9 (1990) and Chemical Abstracts 113: 28332F (KHAN DELWAL et al) see particularly compounds with reg number 128586-89-0	1 to 3, 5 and 6
X	Chemical Abstracts 53: 11397b see particularly compound with reg number 109559-14-0	1 and 6
X	Chemical Abstracts 52: 2748p (MOSCOW UNIV) see particularly compound with reg number 109559-14-0	1 and 6
X	Bull Chem Soc. Japan 58(5) 1413-20 (1988) and Chemical Abstracts 104: 109574g (TOKYO INST TECHNOL) see particularly compound with reg number 100565-01-3	1, 5 and 6

Databases:The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).